invention under low viscosity conditions at the time of the invention particularly in light of subsequent art.

In the previous Office Action, dated December 9, 1997, the Examiner rejected claims 10, 26, 34, 41, and 42 under 35 U.S.C. § 112, second paragraph and claims 22-23 under 35 U.S.C. § 102(b). These claim rejections were not maintained in the Office Action dated July 20, 1999. Accordingly, it is hereby confirmed that these rejections have been withdrawn.

Rejections Under 35 U.S.C. § 112

Claims 1-21, 29, 30, 34-40, 43-50, 53-56, 69 and 70 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being enabling for the claimed method or kit which uses a high viscosity or gel forming medium such as gelatin or agarose or alginate, does not reasonably provide enablement for the claimed method or kit that does not use these ingredients. This rejection is contradicted by the Examiner's own observation that there are conditions under which the claimed invention is effective in a non-viscous medium, the specification and the documented skill of one in the art at the time of filing the specification.

In order to satisfy the requirements of 35 U.S.C. § 112, first paragraph, a patent application must teach one of ordinary skill in the art how to make and use the claimed invention. The enablement requirement is met if the specification enables *any* mode of making and using the claimed invention. Applicants have fulfilled this requirement. The Examiner concedes that the specification is enabling for a preferred embodiment of the claimed invention.[1] As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, then the

[1] In a preferred embodiment, during the secretion phase the cells are incubated in a gelatinous medium, and preferentially the size limitation of penetration into the gel prevents the product from substantially entering the gel.

enablement requirement of section 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Given this rationale alone, the rejection should be withdrawn. It is well established that enablement is not precluded by the need for some experimentation, or, in fact extensive experimentation.

Experiments described in Example 1, the results of which are illustrated in Figure 6b of the specification as originally filed and in the present specification, demonstrate that successful separation of cells on the basis of secreted products was achieved without use of a high viscosity medium. See the Office Action responses dated August 20, 1997 and June 9, 1998. The Examiner has refuted the results of this example, most recently on the ground that "the specification indicates that depending on the parameters used, in the absence of high viscosity medium, it is not possible to distinguish secreting from non-secreting cells." (see page 27 of the Office Action, last paragraph) Read from another perspective, the Examiner's statement says that the specification provides examples of how to make and use the claimed invention and has clearly taught that parameters can be varied in order to do so. The fact that applicants have given conditions where non-viscous medium is effective is sufficient to satisfy § 112. In fact, the cited paragraph and subsequent page of the specification unambiguously teach one of skill in the art that varying incubation time or viscosity allow successful use of the invention.

> Figure 6 shows the resulting staining as FACScan illustrations: duration of entrapment test (6a) 10 min; (6b) 30 min; (6c) 1h; and (6d) 2h. Two populations can be differentiated after 30 min, which have captured different amounts of IgM. The difference between the two populations disappears after lengthy incubation because of IgM given off to the medium by the secreting cells, which is taken up by the entrapment antibodies on the nonsecreting cells.
>
> Entrapment of Secreted IgM Using a Diffusion Inhibitor
>
> It can be seen from the illustration above that the less strongly stained cell population also takes up IgM rapidly on its surface. This background staining comes from secreted IgM in the culture medium that has not been trapped by the entrapment antibodies on the secreting cells. If the entrapment experiment is carried out in a more viscous medium, this background staining can be reduced. Specification page 27, line 26 to page 28, line 9, emphasis added.

Thus, the specification teaches that by varying incubation time or viscosity background staining can be reduced. These variations are well within the skill of one in the art. There is only one other parameter in the method, cell density. Varying all parameters to optimize results is well within the skill of one in the art. Varying three parameters each of which is known to be thermodynamically important, is certainly well within the skill of one in the art. This is especially true where clear instructions are provided on variation of two of the parameters. It is well established that the necessity of even extensive experimentation by one of skill in the art to make and use the invention does not render the invention non-enabling.

Support for this position can be found in the declaration by Dr. Assenmacher, filed on June 12, 1998. The declaration shows how the claimed invention can be practiced in normal medium, using well known methods, including optimization of incubation conditions with respect to cell density and incubation time. It is the Examiner's own interpretation that the Assenmacher declaration introduces "crucial steps." This is not an accurate representation. Varying cell density and time to optimize conditions that are well known to work (see Example 1 of the specification), while perhaps necessary, is well within the skill of one in the art. No new parameters are introduced.

It is well known in the art that cell density has a direct effect on secretion of products. In practicing the claimed invention, one of skill in the art would vary parameters involving cell density, time and medium viscosity to control secretion. It is well known in the art that the length of incubation has a direct effect on methods of affinity-based detection. On page 12, lines 4-24 of the specification, variation of the incubation parameters is specifically contemplated, including variation of the incubation time. In practicing the claimed invention, one of skill in the art would vary all the relevant parameters, including the length of incubation, cell density and medium viscosity to control the affinity-based capture of secreted products. The specification

need not disclose what is well known to those skilled in the art and preferably omits that which is well known. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Much is made of the use of gelatinous medium in the post-filing publication by Manz et al. ("Manz"). The disclosure in the publication is merely one aspect of the claimed invention.[2] See page 5, lines 26-31 and page 13, lines 11-15 of the specification. Manz represents an embodiment of the claimed invention[1], not the entire scope of the claims. In a publication for a scientific journal, Manz would not be expected to reiterate variable incubation parameters well known in the art. If anything, the absence of such a discussion in the publication supports the view that these variations are well within the skill of the art. Quotations from Manz and the specification are provided in the outstanding Office Action to allege that use of viscous medium is always necessary when this is clearly not the case. See page 3, last paragraph of the Office Action. Each quotation references a particular set of exemplary conditions in which use of the gelatinous medium was necessary. Specifically, the Manz quote relied on states that "in the approach described here, [the diffusion product] will label all cells." (emphasis added) As seen in the specification, and highlighted by the Examiner, there are conditions under which a viscous medium is required. This does not mean it is always required. As acknowledged by the Examiner, the specification provides examples where the claimed invention is enabled in the absence of viscous medium.

The incubation period for 10^7 cells used in Manz was 45 minutes. As noted in the specification, 30 minutes incubation with 10^7 cells was optimal in the absence of a viscous medium and a one hour incubation resulted in a loss of resolution. The quotations relied upon by the Examiner are not, nor were they intended to be, true under *every* set of exemplary conditions.

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[2] Still another aspect of the invention is a kit for use in the detection of cells that secrete a desired product, the kit comprising: a material for use in preparing gelatinous cell culture medium, said medium to be used for cell incubation for the production of the desired secreted product...

These quotations are taken out of context and as a result, in each instance, the Examiner argues from the specific to the general. This is not logically defensible and results in erroneous conclusions. The fact that there are inoperable embodiments of the claimed invention is irrelevant to patentability. Given that the specification teaches one of skill in the art how to make and use the claimed invention, the fact that there is an "approach" under which the claims will not be operable does not render the claims non-enabled.

Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that support for the methods in claims 69 and 70 cannot be found in the specification as originally filed. It is well established that what is known by one of skill in the art need not be included in the specification. With respect to claims 69 and 70, one need not look to the specification to find support, but to the state of the art. Bispecific antibodies represent a specific example of a capture moiety. Capture moieties are those which attach both to the cell, either directly or indirectly, and the secreted product. Thus, the capture moiety encompasses a specific binding partner attached to the cell surface. Like capture moieties, label moieties are specific binding partners which attach to the product. Label moieties are either directly or indirectly labeled. Given the skill in the art, simultaneous application of a capture moiety and label moiety, each binding to the same product under presumably similar conditions, would be available to one of skill in the art.

Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 14, 15, 29, 30 stand rejected under 35 U.S.C. § 102(b) as anticipated by Kohler et al ("Kohler"). Applicants respectfully traverse this rejection. In order to sustain a rejection under 35 U.S.C. § 102, the Examiner must show that each and every element of the claimed invention is found in a single reference. The Examiner has failed to fulfill this requirement.

Kohler discloses a method of negative selection wherein a hapten, trinitrophenyl (TNP), is coupled to the surface of cells and those cells which secrete antibody to the cell-surface hapten are lysed upon binding antibody in the presence of the cytotoxic complement. Only cells which either secret mutant antibody or no antibody at all survive. The Examiner has failed to show that the method of Kohler, a method to produce cells which are lysed, is equivalent to the method of claims 14 and 15. The Examiner has failed to and cannot show that the cells in Kohler, the surviving mutant cells, are equivalent to the cells in claims 29 and 30.

Claim 14 has been amended to clarify the labeling step as that in which a label is attached to the secreted product bound to the cell. A method for producing cells which are lysed as a result of the labeling procedure (Kohler) is thus specifically excluded.

The Examiner further alleges that the hybridoma cells in Kohler comprise each and every element of the cells in claims 29 and 30. Claims 29 and 30 include, but are not limited to hybridoma cells. Claims 29 and 30 depend from claim 1 and therefore, comprise only secretory cells for which there is a specific binding partner to serve as an effective capture moiety within the scope of the claims. The progeny of these cells are unique in having been descended from cells specifically selected by the process of the claimed invention. All prior art hybridoma cells were selected by some other method and thus do not anticipate the claimed products. The only viable cells in Kohler are those unlabelled cells which survive as a result of genetic mutations in the immunoglobulin synthetic pathway and are thus not the progeny of the labeled cells. The immunoglobulin synthetic mutant cells in Kohler clearly do not comprise each and every element of the cells in claims 29 and 30.

According to Chisum on Patents, the Patent Office policy is to allow product-by-process claims, even if the invention could be described otherwise, so long as the definiteness requirement is met. Thus, a product may be claimed in terms of the process of making it. The rejections under 35 U.S.C. § 102(b) should be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 14-28, 34-51 are rejected under 35 U.S.C. § 103 as being unpatentable over Kohler, in view of Hunt et al. ("Hunt"), and US 4,676,980 ("Segal"). Applicants respectfully traverse this rejection. Claims 14, 34 and 35 have been amended to clarify that the cells are labeled on the basis of the secreted and bound product. Thus, Kohler is more clearly excluded from the scope of the claims. Kohler, alone or in combination with Hunt and/or Segal, does not render the claimed invention unpatentable.

The above discussion fully responds to the rejections made in the outstanding Office Action. Accordingly, the present claims are in condition for allowance, which is earnestly solicited. If a telephone call would further prosecution of this case, the Examiner is invited to call the undersigned attorney at (212) 468-8186.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 21230. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: January 20, 2000 By:

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